SURGICAL OUTCOME FOLLOWING NEOADJUVANT CHEMORADIOTHERAPY FOR LOCALLY ADVANCED RECTAL CANCER

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CERTIFICATE

Certified that this dissertation titled **"SURGICAL OUTCOME FOLLOWING NEOADJUVANT CHEMORADIOTHERAPY FOR LOCALLY ADVANCED RECTAL CANCER"** is the bonafide record work done by **Dr. Yamini Chitra. V.** during the period 2005-08, done under my guidance and supervision and is submitted in partial fulfillment of the requirement for the M.Ch. (Branch – VI) Surgical Gastroenterology & Proctology, of The Tamil Nadu Dr. M.G.R. Medical University, August 2008 examination.

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Introduction

The potential for curative resection is the most important component of the multimodality management of rectal cancer. In locally advanced rectal cancer lymph node involvement and positive resection margins are common, leading to local recurrence and metastatic disease. Postoperative chemoradiotherapy significantly improves both local control and overall survival. Several studies have shown that preoperative chemoradiotherapy has increased local control rates, sphincter saving procedures and resectability. This study evaluates the potential benefits and outcome following neoadjuvant chemoradiotherapy for locally advanced operable rectal cancer.

Aim

The aim of the study is to analyse the surgical outcome following neoadjuvant chemoradiotherapy in patients with locally advanced operable rectal cancer i.e. T 3, T 4, node positive tumour. Its main aim is to analyse whether

1. It is beneficial to the patient or not.
2. The primary end points analysed are the downsizing of tumour, downstaging of the tumour, sphincter saving rates, toxicity of chemoradiotherapy, patient compliance for the regimen.
3. Secondary end points analysed are the incidence of local recurrence, distant metastasis. The incidence of peroperative complications and postoperative complications are also analysed.

Review of Literature

The main problem in treatment of locally advanced cancer rectum is that many are unresectable or even if resected have a high incidence of local recurrence. Lack of improvement in the surgical results in three decades prompted many investigators to seek different radiotherapeutic approaches in conjunction with surgery. In the1960s and 1970s various American and European clinicians reported favorable, but sometimes conflicting, results on this subject. These results nevertheless gave the impression that preoperative radiotherapy had a place in the management of patients with potentially operable rectal cancer. In 1969, Moertel and Reitemeie P[1] showed that combined radiotherapy and 5- fluorouracil gave significantly better subjective as well as objective results in the management of advanced gastrointestinal malignancies.

Age impacts colorectal cancer incidence more than any other demographic factor. The incidence of sporadic colorectal cancer increases dramatically above the age of 45 or 50 years for all groups. Cancer incidence and mortality rates have been higher in economically advantaged countries. This may be related to consumption of a high-fat and high-red-meat diet, lack of physical activity with resulting obesity, and variations in mortality causes over a longitudinal period of time.

Mode of spread of rectal cancer

Different treatment modalities are available due to various routes of spread, namely direct, lymphatic, venous, transcoelomic or by implantation. Direct spread of rectal tumour can occur in

longditudinal, transverse directions or proximally or distally. Williams et al in 1983 has shown that distal intramural spread greater than one cm is uncommon and when it does occur patients have tumours which are incurable with the available treatment options. There is no substantial evidence to show that a distal resection margin of five cm reduces the chance of local reccurence.

Radial spread from a cancer located on the posterior wall of the rectum may extend through the mesorectum and involve the Waldeyer's fascia. Anterior spread from tumour located below the peritoneal reflection in a male may involve prostrate, seminal vesicle or bladder. Williams et al have shown that leaving residual disease in the pelvis is the main cause for local recurrence.

Lymphatic Spread

Rectal tumour can spread in upward, lateral and downward directions. Distal lymphatic spread is rare and occurs when the upward route is extensively involved. Wide lateral spread occurs in extra peritoneal tumours but is uncommon in tumours above the peritoneal reflection. Discontinuous spread also occurs in about 30 % of cases.

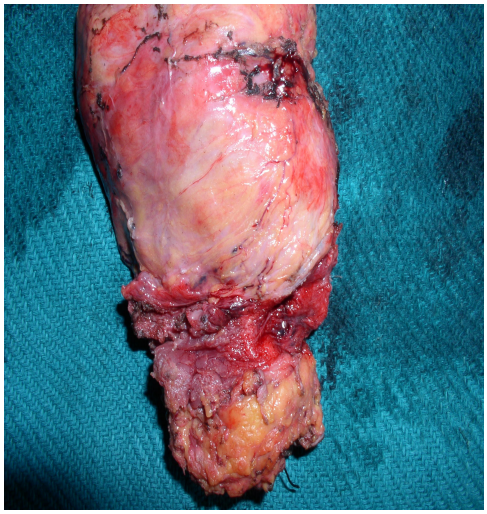
Blood spread can occur to liver, lungs, kidneys, bones and ovary. Greater the incidence and degree of venous invasion worse is the prognosis. Intramural and extra mural veins can be involved and greater the extramural involvement, worse the prognosis.

Local Recurrence in Rectal Cancer

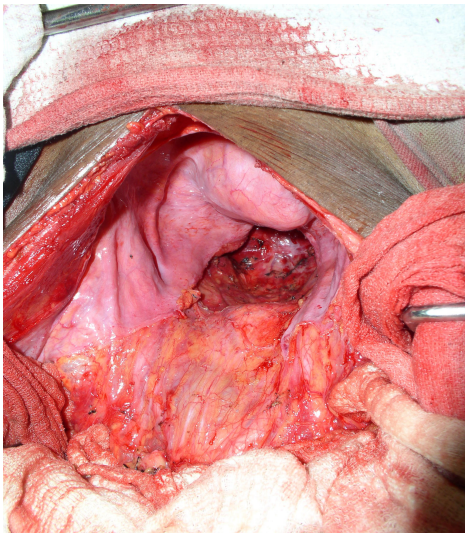
Role of Total Mesorectal excision

Total mesorectal excision is precise sharp dissection around the integral mesentry of the hind gut which envelopes the entire hindgut. By performing this manouvre, all micro metastatic tissue which lie in the mesorectum will be removed enbloc with the rectum and the tumour. The concept of TME was introduced by

TME with intact Fascia Propria



Pelvic cavity post TME



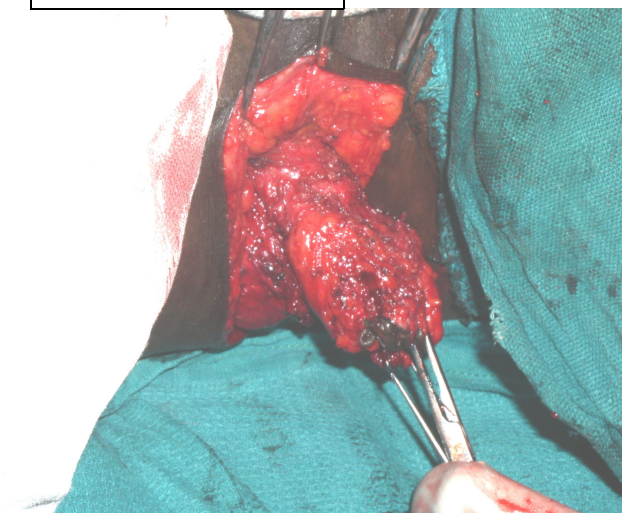
Heald in 1982 [2] .Arbman et al[3] in 1996 compared their results for rectal cancer after adopting the technique of TME with results before using it. They found significant reduction in local recurrence rates ($p<0.03$) and an increase in crude survival ($p <0.03$) at four years in patients who had undergone total mesorectal excision.

So total mesorectal excision should be done for tumours of mid and lower rectum. In upper rectal tumours mesorectum should be removed at least five cm below the palpable edge of the tumour. However such a manouvre is likely to increase the risk of anastamotic leakage because of the danger of rendering the anorectal stump ischaemic. Thus a covering stoma is necessary for all patients undergoing a total mesorectal excision except in patients undergoing abdominoperineal excision of rectum.

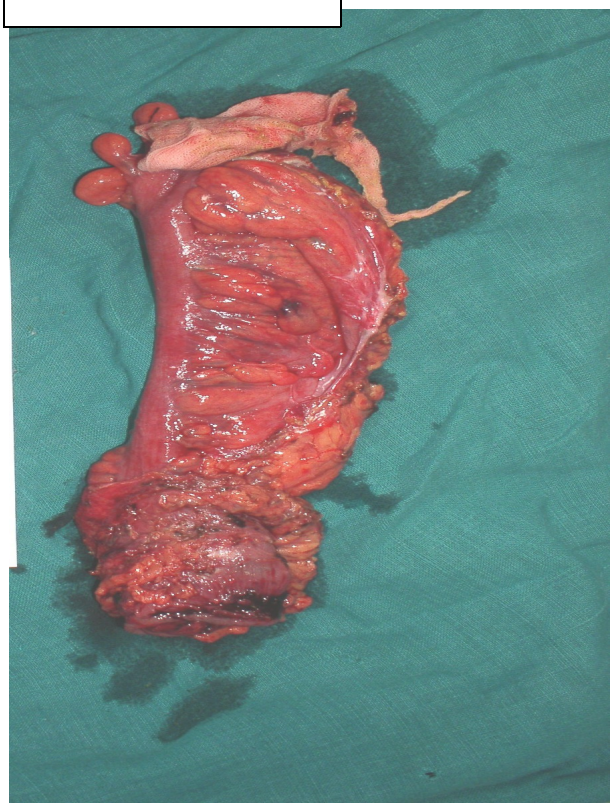
Role of Lateral pelvic lymph node dissection

In rectal cancers,lymphatic spread not only occurs upwards to the mesenteric nodes along the superior rectal and inferior mesenteric vessels, but also laterally to the hypogastric,obturator and nodes along iliac vessels. The incidence ranges from 8.6 to 17.3 % [4.] The local recurrence rate is high and survival is poor in these patients compared with those having positive mesorectal lymph nodes. But extended dissection impairs urinary and male sexual function, resulting in poor

Perineal Dissection



Specimen of APER



quality of life, as the pelvic autonomic nerves are sacrificed during lateral lymph node dissection. Various autonomic nerve preservation procedures have been developed resulting in improved urinary function. Morita[5] et al in 2003 has shown that overall recurrence rate was only 6.3 % and five year survival was 47 %. But even after lateral lymph node dissection, the prognosis of patients with pelvic autonomic plexus involvement was unfavourable.

Jin C Kim et al [6] has compared the outcome between adjuvant postoperative chemoradiotherapy and lateral pelvic lymph node dissection following total mesorectal excision for rectal tumours upto 15 cm from anal verge. There was no difference in overall survival (78 % vs 73.9%) or disease free survival(67.3% vs 68.6 %). But the locoregional reccurrence rate was 2.2 fold higher in the lateral lymph node dissection group than postoperative chemoradiotherapy group(16.7 % vs7.5 5 ,p = 0.044). The addition of lateral lymph node dissection to total mesorectal excision prolonged time in surgery by 90 to 120 minutes and increased the transfusion requirement by more than 50 %. So the authors concluded that even after lateral lymphnode dissection, postoperative chemoradiotherapy was needed to decrease local recurrence. Hence lateral lymphnode dissection is of no added benefit to the patient.

There is a high incidence of locoregional and distal recurrence in locally advanced rectal cancers following only surgical treatment. Various treatment modalities in form of neoadjuvant radiotherapy, adjuvant radiotherapy, adjuvant chemotherapy, adjuvant chemoradiotherapy has been tried.

Patients with rectal cancer can be divided into three main groups. Most patients have resectable cancers. Patients in the next category have borderline resectable disease, that is breached circumferential margins as predicted by imaging studies. Finally, there are patients with fixed unresectable cancers, for whom surgery is not possible without leaving tumor within the pelvis. This group may, after chemoradiotherapy, become respectable.

.In clinically resectable cancers, residual microscopic disease after surgery can persist either at or beyond the surgical resection margins, within lymph nodes, or in distant metastatic sites. In locally advanced rectal cancer (LARC), lymph node involvement and positive resection margins are common, leading to local recurrence and metastatic disease. Both radiotherapy and chemotherapy have been advocated as adjuvant strategies to eradicate cells at the margins or in discontinuous areas of tumor within the pelvis, in nodes, or in distant metastatic sites to improve both local control and also overall survival (OS). In borderline unresectable rectal cancers, a high risk for local recurrence and poor survival have been reported with preoperative radiotherapy alone .This finding illustrates the need for combining therapies that integrate concurrent chemotherapy, radiotherapy, and surgery. Chemotherapy may, as a component of chemoradiotherapy, both act as a radiosensitizing agent and also potentially eradicate distant micrometastases. This strategy has been investigated with different agents in a number of phase I/II and III trials of preoperative neoadjuvant chemoradiotherapy.

Role of preoperative radiotherapy

On administering preoperative radiotherapy the size of primary tumour and the number of nodes involved are reduced. The extent of pathological down grading of tumour achieved varies with the dose of radiation used. This is proved by MRC trial in 1984 were a statistically significant reduction of 30 % of number of nodes involved and negative nodes after a fractionated irradiation of 20 Gy, but no difference was observed between the group which received a single dose of 5 Gy and the control group.

Preoperative radiotherapy also reduces local recurrence. It helps reduce the size and extent of local spread and makes a locally advanced tumour operable incertain cases. But it is associated with high toxicity and abdominal and perineal wound healing is affected. Most of the studies have not shown any improvement in overall survival compared to surgery alone. Preoperative radiotherapy with the aim of improving local control has been studied extensively.

In 1974 Stearns.et al [7] reported on the results in the trial of preoperative radiotherapy, in Memorial Sloan Kettering Cancer Centre in New York. Patients were randomized to receive 20 Gy of preoperative radiotherapy or surgery only. No improvement in overall survival or local recurrence was noted

.

The Veterans administration Oncology Group (VASOG) had 20 Gy given preopatively for two weeks followed by surgery. Additional 5 Gy was given if tumour was within five cm of anal verge. This study showed that there was reduction in number of nodes involved by the tumour after irradiation,down grading of the tumour. There was reduction in local recurrence after radiotherapy in a subgroup who underwent post mortem.

The Swedish Rectal cancer group[8] has shown that short course of radiotherapy of twenty five gray in five fractions over five days followed by surgery in seven days had decreased local reccurrence and improved overall survival(58 % vs 48 % $p < 0.004$).

Role of Radiotherapy in unresectable rectal cancer

For those patients in whom CT suggests that the tumour is unresectable, preoperative radiotherapy either alone or ideally in combination with chemotherapy, is recommended. Preoperative radiotherapy without chemotherapy for such locally advanced tumors using doses of 45–50 Gy was reported to be capable of downstaging 79% of patients, which resulted in high resection rates being achieved. Despite complete resection, the 5-year survival rate was only 18%, and these patients continued to have a high risk for local failure. Patients who remain unresectable after radiotherapy have an even poorer overall median survival duration of only 8–10 months.

Unresectable Rectal Cancer: Randomized Trials of Chemoradiotherapy versus Radiotherapy Alone

In a single small phase III randomized study [9], only 70 patients with fixed inoperable rectal cancer were treated. The chemoradiotherapy delivered an alternating hyperfractionated split-course regimen to a total dose of 40 Gy over 8 weeks in combination with methotrexate, 5-fluorouracil and folinic acid. The trial established an advantage in terms of resectability and local control for the chemoradiotherapy arm.

The local recurrence-free survival rates at 5 years were 35% versus 66% (p.03) and the 5-year survival rates were 18% versus 29% (nonsignificant) for radiotherapy versus chemoradiotherapy, respectively. These data lend support to the view that chemoradiotherapy is more effective than radiotherapy .

However, intensification of the chemoradiotherapy component for patients with T1N0 or

T2N0 rectal cancer may achieve a higher pathological complete response without a longer overall survival. If very low levels of local recurrence is achieved in this group of patients, the risk for metastatic disease will almost certainly predominate.

Facilitating Sphincter-Sparing Procedures

The low rectal cancers (3–6 cm from the anal verge) and bulky anterior tumors in obese men with a narrow pelvis render surgery technically demanding if sphincter-sparing surgery (SPSS) is the aim. Long course chemoradiotherapy followed by a planned delay prior to surgery, may result in shrinkage back from the distal margin, and enable sphincter-sparing surgery.

Impressive results appear to have been achieved in phase II studies with chemoradiotherapy and long term follow-up has confirmed an excellent outcome if marked shrinkage of the distal tumor margin is demonstrated [10.] Subset analysis of randomized trials suggests that preoperative CRT offers a 10% [11] or even a 20%[12] higher chance overall of achieving sphincter-sparing surgery.

Whether a surgeon attempts sphincter-sparing surgery depends on many factors, including tumor size, location, and accessibility, surgical experience and training, and the individual's philosophy regarding risk. A randomized trial investigating short course radiotherapy against preoperative chemoradiotherapy with the endpoint of sphincter-sparing surgery showed no difference[13], surgeons did not change their initial decision.

Preoperative chemoradiotherapy versus Postoperative chemoradiotherapy in Resectable Rectal Cancer

A common randomized trial design compares preoperative chemoradiotherapy with postoperative chemoradiotherapy. There are three trials in this setting - the National Surgical Adjuvant Breast and Bowel Project (NSABP) R03, the Intergroup trial INT-0147, and the German CAO/ARO/AIO-94 trial.

National Surgical Adjuvant Breast and Bowel Project Protocol R-03[14]

It was designed to determine the worth of preoperative chemotherapy and radiation therapy in the management of operable rectal cancer. Patients with primary operable rectal cancer were randomized to receive multimodality therapy preoperatively or after curative surgery . All patients received seven cycles of 5-fluorouracil (FU)/leucovorin (LV) chemotherapy. The preoperative arm (Group 1) received the first three cycles of chemotherapy and all radiation therapy (5,040 cGy) before surgery, and four cycles of chemotherapy post operatively. The postoperative arm (Group 2) received all radiation and chemotherapy after surgery. 5- Fluorouracil and leucovorin chemotherapy was given during the first and fifth week of radiation therapy.

Primary study end points included disease-free survival and overall survival. Secondary end points included local recurrence, primary tumor response to combination therapy, tumor downstaging, and sphincter preservation. Overall treatment-related toxicity was similar in both groups. No patient was deemed inoperable because of progressive local disease. The use of protective colostomy in patients undergoing sphincter-sparing surgery and the development of perioperative complications in all surgical patients were similar in both groups. There was evidence of tumor downstaging in evaluable patients undergoing preoperative therapy, with 8 percent of Group 1 patients having had a pathologic complete response.

The authors concluded that the preoperative chemotherapy and radiation therapy regimen used were safe and tolerable as standard postoperative treatment.

There was a trend to tumor downstaging and sphincter preservation in the preoperative arm. This trial was closed prematurely due to poor accrual after randomizing only 267 patients.

Intergroup trial INT-0147[15]

The Intergroup INT-0147 trial also closed early because of poor accrual, after randomizing only 53 patients. The planned RT dose was 50.4 Gy.

The German CAO/ARO/AIO-94 Trial [12]

The German CAO/ARO/AIO-94 study was initiated in 1995 to investigate preoperative 5-FU–based chemoradiotherapy versus postoperative combined-modality treatment for stage II/III resectable

rectal cancer. The primary endpoints were overall survival and disease free survival and locoregional and distant control. The secondary endpoints included the rates of curative (R0) resections, sphincter-sparing surgery, toxicity, and surgical complications. Results show no greater surgical morbidity for chemoradiotherapy [12].

The locoregional failure rate was lower with preoperative chemoradiotherapy -6%, compared with 13% for the postoperative arm. However, neither the disease free survival nor overall survival rate was greater in the preoperative arm. On subset analysis, a slightly higher sphincter-sparing surgery rate was noted for those patients in whom the surgeon initially felt that an abdominoperineal excision of the rectum was inevitable.

In addition, compliance was low for the postoperative arm, and only 54% received the full radiotherapy dose, compared with 9 2 % in the preoperative arm. Both acute and late toxicities appeared to be less frequent in the preoperative arm, but it should be noted that a 5.4-Gy radiation boost was mandated in the postoperative arm. Patients in the postoperative arm would have received a 10% higher radiotherapy dose. Radiotherapy dose escalation has rarely been evaluated in rectal cancer because of the constraints of acute and late toxicities.

The Lyon R 96–02[16] study used contact therapy to boost external beam radiotherapy with an extra 85 Gy in three fractions. Despite a higher complete clinical response rate and a higher sphincter-sparing surgery rate, there was no difference in terms of locoregional failure or overall survival at 2 years. Dose escalation prior to surgical resection seems an illogical strategy to improve local control. If surgery can achieve a good quality mesorectal excision, then recurrences are likely to lie outside this volume. Consequently, dose escalation of radiotherapy to the primary tumor seems unlikely to achieve much more than a higher rate of acute toxicity.

Preoperative Chemoradiotherapy Versus Radiotherapy Alone

The second strategy has been to randomize between preoperative neoadjuvant chemoradiotherapy and an identical schedule of preoperative radiotherapy alone. One historical and two other recent larger studies have used this design.

In 1984, the European Organization on Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group[1] two-arm randomized clinical trial to compare the efficiency of preoperative administration of radiotherapy with 5-fluorouracil with radiotherapy alone before radical surgery. Two hundred forty-seven eligible patients were admitted from November 1972 through April 1976. Total tumor dose of 34.5 Gy in 15 fractions of 2.3 Gy each over an overall period of 18 days. Patients receiving combined preoperative therapy had intravenous 5-FU injection in the dose of 10 mg per kg of body weight (375 mg/m^2) during the first four days 4 to 6 hours prior to irradiation. Surgery usually followed within 2 weeks after the last irradiation.

The overall survival observed in the group treated with preoperative radiotherapy appeared to be better than in the group of patients where preoperative combined modality was administered. Five-year survival was 59% versus 46% with a marginal statistical significance of P=0.06. Although the combined modality arm had a higher incidence of side effects and postoperative deaths, it had a greater effect than the radiotherapy- alone arm in controlling the disease process, mainly distant metastases to the liver with a result bordering on statistical significance (P=0.07). No difference was observed in local recurrence. Disease free survival was longer in the combined modality group ,though not statistically significant.

The incidence of nonmalignant and intercurrent deaths were higher in the combined modality group, whereas deaths due to malignancy were higher in the radiotherapy alone group. The authors concluded that by observing more stringent selection in disease and patients' criteria, side effects and intercurrent deaths can be effectively reduced with further improvement in adjuvant results.

EORTC 22921 Trial [17]

The EORTC 22921 trial was initiated in 1993 and enrolled 1,011 patients with T3/T4 resectable rectal cancer over 11 years, with endpoints of overall survival and disease free survival. Patients were allocated to the following four arms: arm 1, preop radiotherapy 45 Gy in 5 weeks; arm 2, preop radiotherapy plus two 5-day chemotherapy courses (fluorouracil 350 mg/m^2 /d and leucovorin 20 mg/m^2/d) in the first and fifth week of radiotherapy; arm 3, preop radiotherapy plus four postop chemotherapy courses and arm 4, preop radiotherapy and chemotherapy plus postoperative chemotherapy.

The study examined the role of the timing and duration of 5-FU–based chemotherapy both in combination with preoperative radiotherapy, and in the postoperative adjuvant setting. The trial stratified according to T stage, distance to the anal verge, sex, and institution. Total mesorectal excision (TME) was only recommended in 1999. Compliance with the preoperative chemotherapy was high, but only 42.9% adhered to the postoperative component of chemotherapy.

The addition of preoperative chemotherapy to radiotherapy caused significant down sizing($p < 0.001$), down staging ($p < 0.001$), had smaller number of examined lymph nodes, less

frequent lymphovascular invasions[18]. The toxicity was higher in the chemoradiotherapy arm. The pathological complete response rate was significantly higher in the chemoradiotherapy arm and it appeared to offer a marginal benefit in terms of a higher sphincter-sparing surgery rate (55.6 % versus 52.4 %; p .05). The locoregional failure rates at 5 years were 17% with radiotherapy and 8% with chemoradiotherapy. With a median follow-up of 5.4 years, no significant difference was seen in disease free survival or overall survival between groups that received sphincter-sparing surgery or radiotherapy and those who received further adjuvant chemotherapy postoperatively (p<.12). A major conclusion of the study is that if radiotherapy is given, then 5-FU–based chemotherapy, whether administered concurrently with radiotherapy prior to or following surgery, confers a significant advantage in terms of local control.

Fédération de Francophone de Cancérologie Digestive -FFCD 9203 Trial [19]

The FFCD 9203 trial[19] randomized 762 patients with T3/T4 resectable rectal cancer between pre operative radiotherapy and preoperative chemoradiotherapy to a dose of 45 Gy. The same chemotherapy regimen as in the EORTC trial (5-FU, 350 mg/m^2, and folinic acid) was combined with the same dose of radiotherapy (45 Gy in 25 fractions). The primary endpoint was overall survival. In contrast to the EORTC study, patients were mandated to receive postoperative adjuvant chemotherapy, but compliance was poor and only 70% of patients received it.

Compliance in the preoperative chemoradiotherapy arm was 93%. The rate of grade 3 or 4 acute toxicity was significantly higher in the chemotherapy arm (14.6%, versus 2.7% for radiotherapy alone; p.05). Surgical complications, including anastomotic leaks, were similar in the two arms. Similarly to

the EORTC trial, the pCR rate was higher with chemoradiotherapy, 11.4%, versus 3.6%. There was no impact of chemoradiotherapy on sphincter preservation. A lower local recurrence rate was observed, 8.1%, versus 16.5%. Again, neither disease free survival nor overall survival was significantly different in the two groups. A similar number of patients in each arm developed metastatic disease (99 following radiotherapy and 107 following chemoradiotherapy).

This trial claims that, from 1999, the majority of patients were treated with TME and the local recurrence rate was reduced to 14% for radiotherapy alone and 5% for chemoradiotherapy.

The Polish Trial [13]

The Polish study [13] randomized 316 patients between preoperative long fractionation chemoradiotherapy (50.4Gy in 28 daily fractions with 5-FU and folinic acid) and short course preoperative radiotherapy. The trial aimed to evaluate whether long course chemoradiotherapy with an interval to allow response could facilitate sphincter-sparing surgery when compared with five fractions of short-course radiotherapy and immediate surgery. Sphincter-sparing surgery was the main endpoint. It is the first time that a long fractionation chemoradiotherapy regimen has been directly compared with short course preoperative radiotherapy. The pathological complete response rate was 15% in the chemoradiotherapy arm, compared with only 1% in the short course preoperative radiotherapy arm, but this did not impact sphincter preservation—61% in the short course preoperative radiotherapy arm versus 58% in the chemoradiotherapy arm (p=0.57). Crucially, this trial reported a difference in curative resection rates for the two strategies.

A circumferential resection margin of 1 mm was observed in 4% of patients after chemoradiotherapy versus 13% of patients after short course preoperative radiotherapy. The local failure rate was 11% after short course preoperative radiotherapy versus 16% in the chemoradiotherapy arm, although these are not significantly different. There was no difference in disease free survival and overall survival.

The addition of 5-FU based chemotherapy to neoadjuvant radiotherapy in the recent European randomized trials of rectal cancer led to significantly better tumor downstaging, pathological complete response, and local control than with radiotherapy alone, but it does not translate into a benefit in terms of longer disease free survival and overall survival, nor a higher chance of sphincter preservation. Metastatic disease remains a significant problem. Adding a second drug (mitomycin C, oxaliplatin, or irinotecan) results in a higher pathological complete response rate, and could be more effective in killing micro metastases, but this strategy has not yet been demonstrated to result in longer disease free survival and overall survival.

Material and Methods

This study was conducted in the Department of Surgical Gastroenterology, Madras Medical college, Chennai.

Study period

From September 2005 to April 2008

Eligibility Criteria

1. All patients with locally advanced operable rectal cancer i.e. T 3, T 4, node positive tumours without distant metastasis

2. Patients with histologically confirmed adenocarcinoma within 12 cm from anal verge.

Exclusion Criteria

1. Patients who previously had cancer other than basal cell carcinoma of skin,
2. Patients who had received chemotherapy or radiotherapy
3. Patients with contraindications to chemoradiotherapy
4. Tumour involving pelvic side walls,upper sacral vetebra, involving upper rectum
5. Distant metastasis .

The study was approved by the medical ethics committee of the hospital.

Preoperative evaluation

After obtaining informed written consent, patients were enrolled into the study.

Locoregional staging was done with contrast enhanced CT of abdomen and pelvis, endorectal ultrasound and cystoscopy in cases suspected of bladder invasion. A lymph node metastasis of four or greater than four as detected by imaging was staged as N 2 disease. Distant metastasis was excluded by contrast enhanced CT of abdomen and pelvis, chest X-ray and if necessary a CT chest. Colonoscopy was done to rule out synchronous lesions.

A basic work up including complete hemogram, renal function tests, liver function tests, and cardiac tests like ECG was done to rule out any major illness and to confirm the patient's fitness for surgery.

Treatment

Preoperative external beam radiotherapy was given for a total dose of 45 Gy in 25 fractions of 180 cGy each, five times per week for total duration of five weeks. It was given as anterior and posterior opposed portals using Telecobalt machine of 1.33 meV. The radiotherapy was given to include the tumour area and its drainage lymph nodes (pelvic-internal, external iliac, obturator). The upper margin of radiotherapy field was L 5-S 1. The lower margin was obturator foramen,1.5 cm below lower border of pubic symphysis. The lateral margin was 1 cm lateral to true pelvis at level of mid inguinal point. If the tumour extended to anal canal, inguinal nodes were included in the field, laterally the radiotherapy field was extended to anterior superior iliac spine.

The chemotherapeutic agent used was 5 Flurouracil, used as a bolus of 350 mg/m ^{2} /d for 5

days, during the first and fifth weeks of radiotherapy along with 20 mg/m^2 of leucovorin. Postoperatively 5 Flurouracil was given for four cycles (350mg/m^2/d,five times weekly once in four weeks) started four weeks after surgery.

Surgery

Patients were assessed five weeks after surgery regarding the progression of the disease. Decision for abdominoperineal excision of rectum , an anterior resection or pelvic exenteration was made preoperatively and modified according to the peroperative findings. Total mesorectal excision was done in patients according to the standardized technique. All patients who underwent anterior resection had a protective ileostomy. Patients with locally advanced unresectable disease underwent only colostomy.

During therapy, patients were monitored weekly for signs of acute toxic effects requiring change in dosage or regimen. Acute and long term toxic effects were graded according to the Radiation Therapy Oncology Group criteria with respect to acute and late adverse effects of radiotherapy. Peroperative and postoperative complications assessed included bleeding, ileus, intestinal fistulas, intra-abdominal abscess, perineal wound complications, urinary retention and death.

Follow up

Patients were followed at three monthly intervals for two years and then at six monthly intervals. Evaluations consisted of physical examination, a complete blood count and blood chemical analysis, proctoscopy, abdominal ultrasonography, CT of abdomen and chest radiography. Local recurrence was to be confirmed histopathologically or by sequential radiological studies to detect enlargement of mass. Distal recurrence was confirmed histopathlogically.

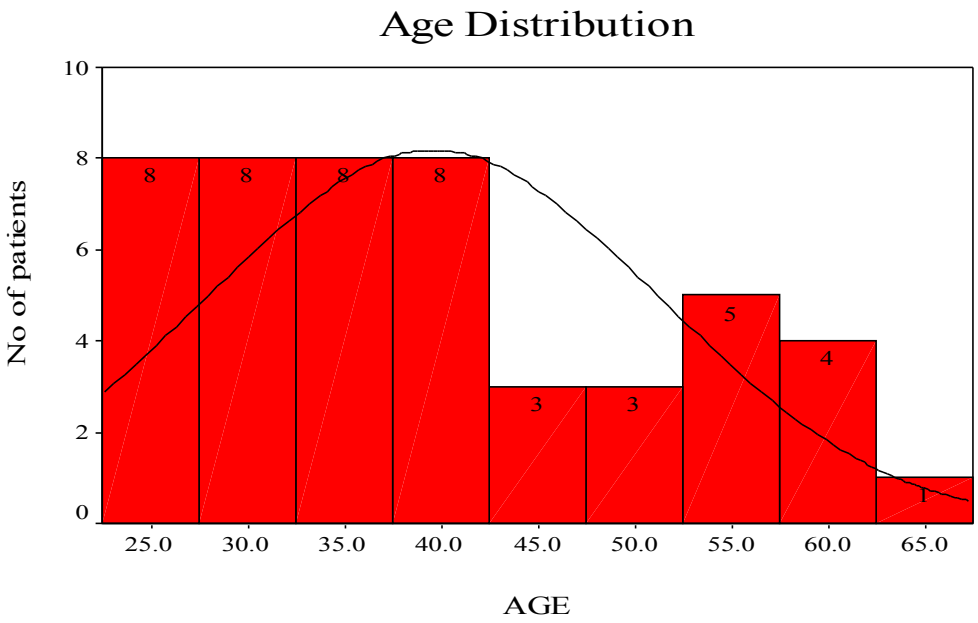
All resected specimens were examined for histological grade, degree of fibrosis, resected margin status and nodal status. The primary end points analysed were downsizing of tumour, downstaging of the tumour, sphincter saving rates, toxicity of chemoradiotherapy, and patient compliance for the regimen. Secondary end points analysed were the incidence of local recurrence, distal metastasis.

Downsizing was defined as a reduction in the size of tumour after chemoradiotherapy as determined by physical examination. Downstaging was defined as decrease in TNM stage, as assessed after chemoradiotherapy in the surgically resected specimen.

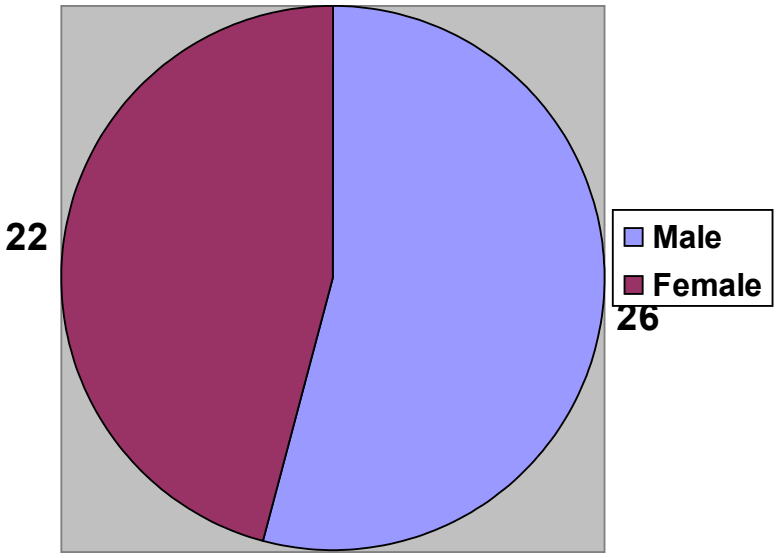
Results

From September 2005 to April 2008, fifty five patients were enrolled in the study. Seven patients dropped out during various phases of treatment, three patients during radiotherapy after three weeks of treatment when their rectal bleed stopped, four patients after completion of chemoradiotherapy. Forty eight patients underwent surgery post chemoradiotherapy. Their demographic characters are presented below.

Age	Mean 39.58 yrs Range 24-61 yrs
Sex	Male 26 (54.16%) Female 22 (45.84%)



Sex Distribution



Distance from anal verge	No (%)
0-4 cm	32 (66.6 %)
4-8 cm	15 (31.32 %)
8-12 cm	1 (2.08 %)

Patients age ranged from 24-61 yrs, mean age being 39.58 years. Twenty six were males and 22 were females. Most of the tumours extended into anal canal (66.6 %). Fifteen patients had tumours involving lower rectum and one had tumour involving middle rectum.

Tumour Characteristics

Clinical Stage of Tumour	No (%)
Stage 1 (T1,T 2, N0,M0)	0
Stage 2 A (T3, N0, M0)	4 (8.33 %)
Stage 2 B (T4, N0, M0)	1(2.08 %)
Stage 3 A (T1, T2, N1, M0)	0

Stage 3 B (T3, T4, N1, M0)	36 (75 %)
Stage 3 C (any T, N2, M0)	7 (14.58 %)
Stage 4 (any T, any N, M 1)	0

Pre operative Histology	**No (%)**
Well Differentiated	23 (48 %)
Moderately Differentiated	19 (39.5 %)
Poorly Differentiated	6 (12.5 %)

Thirty six patients had stage 3 B disease and seven had stage 3 C disease. Endorectal ultrasound was possible only in sixty percent of patients (twenty nine). Forty eight percent of patients had well differentiated carcinoma and thirty nine percent had moderately differentiated tumours. The interval from chemo radiotherapy to surgery ranged from six to nine weeks. The surgeries performed ranged from anterior resection, with concomitant hysterectomy to abdominoperineal excision of rectum.

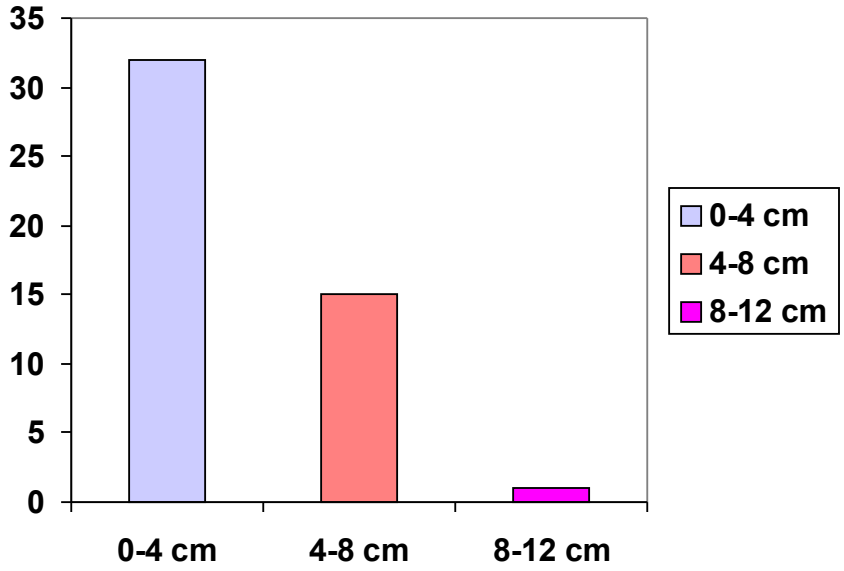
Surgical Data

Interval to Surgery in weeks	**No of cases**
6	24
7	17
8	6
9	1

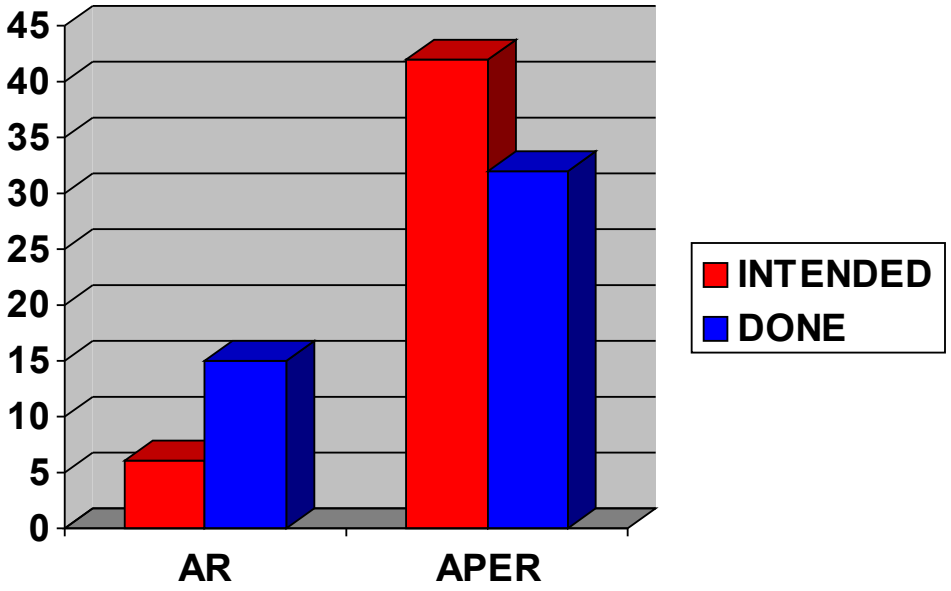
Type of surgery	**No of cases**

Anterior Resection	13
Anterior Resection with adjacent organ resection	2
Abdominoperineal resection	32
Colostomy alone	1

Distance from anal verge



Surgeries Done



Twenty four patients underwent surgery at six weeks after chemoradiotherapy, seventeen patients seven weeks post chemoradiotherapy. In one patient, surgery was done at nine weeks as she had developed respiratory infection and surgery was delayed. Thirteen patients underwent anterior resection, two patients had uterine involvement and underwent concomitant hysterectomy and posterior vaginectomy. Thirty two patients underwent abdominoperineal resection .In one patient growth had extended up to pelvic side wall, was inoperable and a palliative sigmoid colostomy was done.

Complications

Peroperative complications	
Bleeding	1 (2.08 %)

Post operative complications	8 (16.66 %)
Abdominal wound infection	5 (10.41 %)
Perineal wound infection	1 (2.08 %)
Intraabdominal abscess	1 (2.08 %)
Urinary retention	1 (2.08 %)
Chemoradiotherapy toxicity	8 (16.66 %)
Mild-Skin irritation & discoloration	5 (10.41 %)
Vomiting	2 (4.16 %)
Diarrrhoea	1 (2.08 %)
Severe – Anaemia	1 (2.08 %)

One patient developed intraoperative bleeding due to injury to sacral plexus. It was controlled by placing a tacker in the sacral ostia. Minor complications occurred in eight patients, five developed abdominal wound infection which was treated conservatively. One patient developed perineal wound gaping treated with regular dressings. One patient developed abscess in left iliac fossa which was drained under ultrasonic guidance. One patient developed urinary retention in the postoperative period, was treated with continous bladder drainage for 3 months followed by intermittent self catheterization for another month. She had complete recovery 4 months after surgery.

One patient developed anaemia requiring blood transfusion after the second dose of chemotherapy in the fifth week. Minor complications like skin irritation occurred in five patients,

vomiting in two, diarrrhoea in one.

Results of Surgery

Downsizing of Tumour	46/48 p (<0.0001)
Downstaging of Tumour	39/48 p (<0.0001)
Followup Period	6 months-2 yr 2 months (median- 9 months)
Local reccurence	Nil
Distant metastasis	1/48 (2.08 %)

Forty six of forty eight patients had responded well to neoadjuvant chemoradiotherapy with downsizing of tumour .(p value <0.0001). Downstaging occurred in thirty nine (p< 0.0001). The follow up period ranged from six months to twenty six months ,with the median follow up period being nine months. No patient developed local recurrence. Liver metastasis occurred in one patient who had disease progression up to pelvic side walls and was hence inoperable.

APER intended	Sphincter saving procedure done
42	10/42 (23.8 %)

Of forty two patients for whom APER was planned, a sphincter conservation surgery was possible in ten of them after neoadjuvant chemoradiotherapy. Before neoadjuvant chemoradiotherapy only six anterior resections were planned. After it, fifteen anterior resections were done.

Anterior resections intended	Anterior resections done
6(12.5 %)	15 (31.5 %) P = 0.001

Neoadjuvant chemoradiotherapy increased sphincter conservation from 12.5% to 31.5%.

Post operative TNM staging

Stage 1 (T1, T2, N0, M0)	11 (22.91 %)
Stage 2 A (T3, N0, M0)	16 (33.33%)
Stage 2 B (T4, N0, M0)	0
Stage 3 A (T1, T2, N1, M0)	3 (6.25 %)
Stage 3 B (T3, T4, N1, M0)	17 (35.42 %)
Stage 3 C (any T, N2, M0)	1 (2.08 %)

Stage 4 (any T, any N, M1)	0

Patient compliance

Forty eight out of fifty five patients had a complete course of chemoradiotherapy followed by surgery (87.27 %).

Statistical Analysis

Statistical analysis was done using SPSS version 11.4 software and SAF software. The categorical variables were tested using test of one proportion and chi square test. A p value of less than 0.05 was considered statistically significant.

Discussion

Significant advances have been made in the study of colorectal cancer over the last few years. A more thorough understanding of the molecular basis for this disease, coupled with the development of new therapeutic approaches, has dramatically altered the way in which patients are managed. New strategies for screening and for the detection of recurrent disease have also impacted the way physicians approach the workup and disease staging of their patients.

Preoperative Chemoradiotherapy

In resectable rectal cancers the rationale for giving preoperative chemoradiotherapy is not only to improve the survival but also on the potential advantage of delivering both the agents preoperatively. These advantages include improved compliance with the chemotherapy regimen if it is given before a major surgery as well as downstaging which may enhance the rate of curative surgery and permit sphincter preservation in low lying rectal tumours. In addition, because the tumour oxygenation is better if given preoperatively, irradiation is more effective when given preoperatively.

The rates of sphincter conservation surgery is also doubled after preoperative chemoradiotherapy. Postponing the surgery to six weeks later helps shrinkage of tumour and recovery of tissues after treatment. The addition of 5-FU to preoperative radiotherapy produces a higher pathological complete response (pCR) rate over radiotherapy alone[13], and there is evidence for better locoregional control, but no improvement in disease-free survival (DFS) or overall survival has been demonstrated. Distant metastases occur in at least 30% of cases.

Nevertheless, because of the better pCR and locoregional control rates, 5-FU–based preoperative chemoradiotherapy followed by total mesorectal excision has become the standard of care in patients with locally advanced rectal cancer.

More recently, oxaliplatin and irinotecan have been explored within a chemoradiotherapy schedule to increase tumor shrinkage prior to surgery and potentially mirror the success of oxaliplatin in dealing with distant micrometastases in colon cancer. Current chemoradiotherapy schedules have been empirically developed. There is no widely accepted optimal schedule, sequence, and timing, either in terms of the drugs or RT dose.

Radical pelvic RT at doses of 55–60 Gy is associated with high levels of normal tissue damage, including small bowel injury, rectal bleeding, impaired sphincter function, vaginal stenosis, nerve dysfunction, and sacral fractures. Lower radiotherapy doses, 40–50 Gy in 1.8- to 2.0-Gy fractions, are associated with a good tumor response and with more acceptable levels of late morbidity. These doses have become established as a standard.

Downsizing of tumour

Study	**Downsizing**	**p value**
Polish Trial [13] 2004	Present	$p < 0.001$
German Rectal Cancer Study group[12] 2004	Present	$p < 0.001$
EORTC trial 22921[17]	Present	$p < 0.001$

2005		
This study	Present	95.8 % p < 0.0001

Neoadjuvant chemoradiotherapy helps significant downsizing of tumour as it causes tumour shrinkage. In this study downsizing occurred in forty six of forty

Post RT fibrosis in APER Specimen

eight patients (95.8 %), $p < 0.0001$. This is in accordance with other studies which have shown similar significant regression of the tumour after chemoradiotherapy. In one patient he had a poorly differentiated adenocarcinoma infilterating the bladder anteriorly. An anterior pelvic exenteration was planned for this patient after preoperative chemoradiotherapy .But the tumour had extended to the pelvic side walls following treatment and was inoperable and a palliative colostomy was done. He developed liver metastasis in seven months. Another patient had tumour progression into the anal canal necessitating an abdominoperineal excision of rectum. Downsizing is a indicator of good response to preoperative chemoradiotherapy. This is concurrence with the results of Polish trial [13] the tumour was 1.9 cm smaller in patients after chemoradiotherapy.

Downstaging of tumour

Study	**Down Staging**	**Percentage of patients downstaged**
Rich et al [20], 1995	Present	64 % p <0 .01
German Rectal Cancer Group Trial [12] 2004	Present	62 % p < 0.001
EORTC Trial 22921 [17] 2005	Present	52 % p < 0.001
Chung Wah Lam et al [4] 2005	Present	69 % p <0.01 %
This study	Present	83.3 % p < 0.0001

After preoperative chemoradiotherapy, postoperative histopathology shows downgrading of the tumour. In this study thirty nine of forty eight patients (83.3%) showed downstaging ($p < 0.0001$). A good pathological response is a good prognostic indicator, with patients having a good response having less incidence of local recurrence and improved overall survival. Chung Wah Lam et al [4] in 2005 has shown that 69 % of his patients had decreased tumour stages after chemoradiotherapy.

Stage	Preoperative TNM	Postoperative TNM
Stage 1 (T1,2, N0, M0)	0	11 (22.91 %)
Stage 2 A(T3, N0, M0)	4 (8.33%)	16 (33.33%)
Stage 2 B (T4, N0, M0)	1 (2.08 %)	0
Stage 3A (T1, T2, N1, M0)	0	3 (6.25 %)
Stage 3B (T3, T4, N1, M0)	36 (75 %)	17 (35.42 %)
Stage 3 C (any T, N2, M0)	7 (14.58 %)	1 (2.08 %)
Stage 4 (any T, any N, M1)	0	0

Preoperative TNM Staging Vs Post operative TNM Staging

This Study

In this study preoperatively around 75 % of the tumours were in stage 3 B. Post operative

histopathology showed a significant shift towards lower stages stage 2A in 33.33% and 22.91 % in stage 1. The decrease from 75 % to 35 % shows clearly the benefit of preoperative chemoradiotherapy. Due to the tumoricidal effect of chemoradiotherapy the lymph node positivity was reduced from 89.5 % to 43.75 %.

Effect of time interval on surgery and downstaging

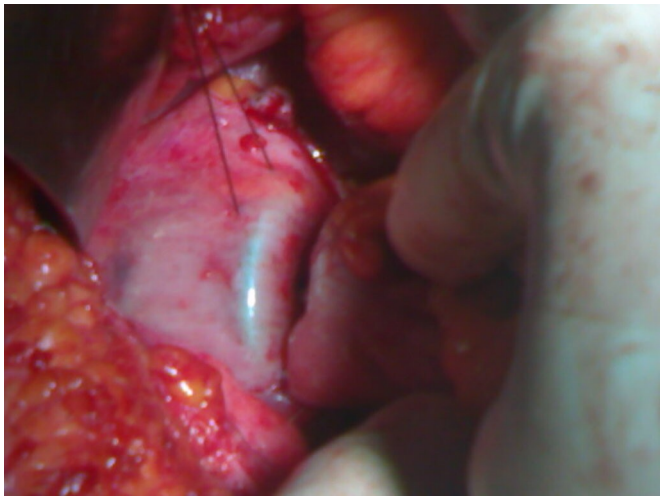
When the optimum time interval between radiotherapy and surgery was analysed non randomized retrospective data led to the hypothesis that a long time interval between radiotherapy and surgery led to sphincter preservation because of tumour downstaging. Francois et al [21] in 1999, conducted a randomized trial to compare short interval outcome with long interval of 6-8 weeks. A long interval between preoperative radiotherapy and surgery was associated with a significantly better clinical tumor response (53.1% in the SI groupv 71.7% in the LI group, P.007) and pathologic downstaging (10.3% in the SI group v 26% in the LI group, P .005). At a median follow-up of 33 months, there were no differences in morbidity, local relapse, and short-term survival between the two groups.

Sphincter-preserving surgery was performed in 76% of cases in the LI group versus 68% in the SI group ($p < 0.27$).He concluded that a long interval between preoperative irradiation and surgery provides increased tumor downstaging with no detrimental effect on toxicity and early clinical results. When sphincter preservation is questionable, a long interval may increase the chance of a successful sphincter-saving surgery.

The ideal time interval is 6 weeks following surgery when there is an optimal tumour response and further delay does not enhance the effect of radiotherapy. When fibrosis sets in, dissection also becomes technically difficult with increased incidence of complications like intra abdominal sepsis, increased bleeding etc. In this study, the interval ranged from 6 to nine weeks, median being six weeks.

Stapled Anterior Resection

Stapled Anterior Resection



Doughnuts after Anterior Resection

Sphincter Saving Procedures after neoadjuvant chemoradiotherapy

Study	Sphincter saving	Percentage
Rich et al [20] 1995	Present	66.6 %
NSABP Trial [14] 1997	Present	50 %
Polish Trial [13] 2004	Present	58 %
German Rectal Cancer Group Trial [12] 2004	Present	39 %
Chung Wah Lam et al [4] 2005	Present	82 %
This study	Present	31.5 %

One of the advantages of preoperative chemoradiotherapy is that tumour downsizing helps sphincter saving procedures possible. The incidence of sphincter saving procedures range from 39 % up to 82 %. In this study, preoperatively only six patients were planned for an anterior resection. After neoadjuvant therapy, anterior resection was possible in fifteen patients, sphincter conservation rates were increased from 12.5 % to 31.5 % ($p < 0.001$) .The lower number of sphincter saving procedures is due to the fact that most of the tumours (66.6 %) had already exrended into the anal canal, hence necessitating abdominoperineal excision of rectum.

Distal Resection Margin after Neoadjuvant chemoradiotherapy

Despite the increasing use of sphincter preservation for rectal cancers, nearly 50% of patients

still undergo abdominoperineal excision of rectum. In many circumstances, abdominoperineal excision of rectum is performed out of concern for adequate distal margins despite mounting evidence that more limited distal margins may be appropriate. For low lying rectal tumours doing an abdominoperineal excision does not increase the radicality of the procedure or improve survival Although distal margins as great as 5 cm were advocated in the past, Paty et al found no increase in pelvic recurrence when the distal margin was <2 cm compared with > 2 cm.More recent data suggest that 1 cm distal margins are adequate [2,22].

A number of clinical pathological studies [2,22] that examined distal intramural spread suggest that smaller distal margins, even 1 cm, may be adequate in the majority of cases. This is supported by pathological evidence that distal intramural spread rarely exceeds 1. When significant distal spread does occur, long-term survival is affected adversely, despite treatment with abdominoperineal excision of rectum. The presence of distal spread is associated with decreased survival primarily due to distant disease recurrence. Although mounting evidence supports the use of 1-cm distal margins in rectal cancer resections, the use of centimeter and subcentimeter margins is controversial.

Jose G Guillem et al [23] on prospective pathological analysis of whole mount sections of rectal cancer following combined modality therapy in 109 patients has shown that intramural extension occurred only in 1.8 % patients (<0.95 cm). Hence he concluded 1 cm margins are sufficient after preoperative chemoradiotherapy and this increases the chances of sphincter preservation without increasing the chances of local recurrence.

Preoperative chemoradiotherapy also reduces circumferential resection margin positivity.

Circumferential resection margin positivity is as high as 25 % if no preoperative chemoradiotherapy is used. In this study a distal margin of one cm did not result in margin positivity in any of the postoperatively examined specimens.

Local Recurrence

Study	**Duration of follow up**	**Local Recurrence**	**Percentage**
EORTC Trial [1] 1984	7 years	Present	15 %
Rich et al [20] 1995	2 years,3 months	Present	4 %
Polish Trial [13] 2004	4 years	Present	14.2 %
German Rectal Cancer Group Trial [12] 2004	4 years	Present	6 %
EORTC Trial 22921 [17] 2005	5.4 years	Present	8 %
Chung Wah Lam et al [4] 2005	12.5 months	Present	13.6 %
Jean Pierre Gerard et al [19] FFCD 9203, 2006	81 months	Present	8.1 %
This study	9 months	Nil	0 %

Local recurrence depends on multitude of factors like stage of the tumour. Tumours that are locally extensive are far more likely to recur than those that are mobile, no matter which type of procedure is performed. The frequency of local recurrence is significantly higher in patients who have circumferential involvement than those without involvement. Recurrence is also influenced by site of lesion in rectum, lower one third tumours have higher incidence than upper third tumours. Incomplete

removal of tumour is a very important cause for local recurrence

Stage of the disease, preoperative therapy used, surgical technique whether TME is used or not influences local recurrence. Local recurrence ranges from 5 .8 % as reported by Kapitjein et al [24] to 15 %. This study during a follow up ranging from 6 months to twenty six months has had no evidence of local recurrence. This correlates well with the excellent response to chemoradiotherapy and an adequate TME as evidenced by downstaging and downsizing.

The use of TME also must be considered as a contributing factor in reducing pelvic recurrences to as low as 5% to 8% in high-risk patients [2]. Quirke et al. demonstrated that radial spread into the mesorectum is a common occurrence. Sharp dissection along the parietal pelvic fascia ensures resection of these small (5 mm) occult nodal metastases that otherwise might be left behind. Radial margins are a more important predictor of disease recurrence and survival than distal margins.

There is an increased risk of recurrence for patients who undergo have abdominoperineal excision of rectum as described previously and likely reflects the worse prognosis attributed to tumors of the low rectum compared with midrectal tumors. The location of the tumor may be a more important prognostic factor than the type of operation performed.

Toxicity of chemoradiotherapy

Study	Mild Toxicity (%)	Severe Toxicity(%)
German Rectal Cancer	12	27

Group Trial [12] 2004		
EORTC Trial 22921 [17] 2005	38.4	13.9
This study	16.66	2.08

About 16.6 % of patients developed toxicity of chemoradiotherapy. Skin irritation and discoloration was the most common toxicity encountered. It was totally reversed after few weeks. This is comparable with other studies showing a range of 11 % to 15 %. The EORTC 22921[17] trial showed a very high toxicity of 38.4 %. In this study no patient had a change in the chemoradiotherapy schedule due to toxicity.

Postoperative complications

Study	**Complications(%)**
German Rectal Cancer Group Trial [12] 2004	36
EORTC Trial 22921 [17] 2005	22.8
Jean Pierre Gerard et al [19] FFCD 9203, 2006	20.9
This study	16.66

There is always a fear that neoadjuvant chemoradiotherapy increases preoperative complications, delays wound healing, patients may need perineal flap cover to prevent post operative wound disruption. The postoperative complications in this study was 16.66 % only. Of 32 patients who

underwent only on abdominoperineal excision of rectum only one developed perineal wound complication which was successfully treated conservatively. So preoperative chemoradiotherapy can be given safely with good patient compliance, minimal side effects and less postoperative complications.

Effect on survival

Most of the randomized controlled studies have not shown any significant survival benefit compared to preoperative radiotherapy alone. Jose G.Guilem et al [25] analysed the long term outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer. With a median follow-up of 44 months, the estimated 10-year overall survival was 58% and 10 year recurrence-free survival (RFS) was 62%. On analysis, pathologic response of greater than 95%, lymphovascular invasion and/or perineural invasion (PNI), and positive lymph nodes were significantly associated with overall survival and disease free survival. Patients with a 95% pathologic response had a significantly improved overall survival ($p < 0.003$) and disease free survival ($p < 0.002$).

Rectal cancer recurrence may be delayed following preoperative chemoradiotherapy and TME and that surveillance of more than 5 years may be warranted. The treatment of locally advanced rectal cancer with preoperative chemoradiotherapy and radical rectal resection with TME currently provides the optimal treatment standard for a durable long-term oncologic outcome in properly selected patients

CONCLUSION

Neoadjuvant chemoradiotherapy given in operable locally advanced mid and low rectal cancers causes significant downsizing, downstaging of the tumour, increases the rate of sphincter conservation surgeries. The toxicity of chemoradiotherapy is minimal, patient compliance is good. The postoperative complications are not increased and it helps decrease the incidence of local recurrence .The effect on survival has to be determined on long term follow up only. Hence it is beneficial to administer it to patients with locally advanced operable mid and low rectal cancers.

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Proforma

Name

Age

Sex

Distance of tumour from anal verge

Diarrhoea				
Small Bowel obstruction	0-4 cm	4-8 cm	8-12 cm	> 12 cm
Stricture at anastamotic site				
Bladder dysfunction				

ERUS; Possible / Not possible

Findings ;

Preoperative Histology :

CECT Abdomen & Pelvis ;

Colonoscopy :

Cystoscopy :

X Ray Chest :

Clinical TNM:

Chemo radiotherapy compliance: Yes / No

Toxicity of Chemo radiotherapy

Acute

Diarrhoea
Dermatological
Hematological

Chronic

Time interval from Chemo radiotherapy to surgery :

Post Chemoradiotherapy Staging :

Downsizing : Yes / No / Increased in size

Type of surgery : AR / APER / Hysterectomy / anterior exenteration / posterior exenteration / inoperable

Use of protective ostomy : Yes / No

Findings at surgery ;

Peroperative Complications ;

Difficulty in dissection :

Bleeding & blood loss :

Postoperative HPE ; Response complete / partial / none

TNM

Post operative Complications

Complication	Yes	No
Ileus		
Wound infection		
Intra abdominal abscess		
Non healing perineum		
Rectovaginal Fistula		
Urinary tract infection		
Urinary retention		
ARDS		
Aspiration		
SI obstruction		
Retrograde ejaculation		
Ventral hernia		

Length of hospital stay :

30 day mortality :

Follow up :

Period	3 months	6 months	9 months	12 months
Physical examination				
Radiological investigations				
Inference				

Period	15 months	18 months	21 months	24 months
Physical examination				
Radiological investigations				
Inference				